New York Times reporter Helene Cooper (right) participates in Moderna's vaccine efficacy trial in Washington, D.C.

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IN DEPTH

COVID-19

Vaccine wagers on coronavirus surface protein pay off

Moderna reports early evidence of excellent efficacy, moving its mRNA candidate closer to widespread use

By **Jon Cohen**

Designers of COVID-19 vaccines appear to have made a spectacularly successful bet. When devising a vaccine against a virus, scientists choose ways to mimic it that they hope will safely teach the immune system how to defeat the foreign invader. For COVID-19, most developers gambled on spike, the protein that allows SARS-CoV-2 to dock onto and infect cells. This week's announcement by the biotech Moderna that its COVID-19 vaccine powerfully protected people from the disease in an efficacy trial was the strongest sign yet that spike is a winning hand.

Since 9 November, Moderna, the pharma giant Pfizer and its German collaborator BioNTech, and a Russian institute have all offered preliminary evidence that spike-based vaccines can achieve greater than 90% efficacy. Because the vast majority of remaining COVID-19 vaccine candidates are also designed to deliver spike—either via its genetic code or the protein itself—the good news may keep arriving. Anthony Fauci, head of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), says he's "optimistic that all the vaccines are going to have very favorable results." He adds that the strong early reports suggest SARS-CoV-2 is not a particularly formidable foe for a vaccine.

No COVID-19 vaccine efficacy trial has yet to cross the finish line, but the details Moderna provided in a press release impressed many scientists. An independent board monitoring its 30,000-person vaccine trial met on 8 November and reported to the company and U.S. government health officials that only five people in the vaccinated group had developed confirmed cases of COVID-19, whereas 90 people who received placebo shots became ill with the disease. That 94.5% efficacy matched the "greater than 90%" interim figure reported by Pfizer and BioNTech and the 92% claimed for a Russian candidate. (That vaccine uses viral vectors to deliver the spike gene but its announced success was based on only 20 COVID-19 cases and drew skepticism in many quarters.) If those numbers translate into equally high levels of real-world protection, then COVID-19 vaccines could rapidly stop the pandemic when widely distributed.

Moderna's "efficacy is just beautiful, and there's no question about the veracity of it either," says Lawrence Corey, a virologist at the Fred Hutchinson Cancer Research Center who co-led the clinical trials network that is testing the candidate.

Moderna offered compelling evidence that its candidate did more than just prevent symptomatic disease, the main endpoint for its trial. The company reported that 11 people in the trial's placebo arm developed severe cases of COVID-19, whereas no one in the vaccinated group did. The vaccine, which like the Pfizer/BioNTech candidate uses messenger RNA (mRNA) to produce spike inside cells, appears to work equally well in all populations studied, Moderna said, including the elderly and ethnic minorities, and people with conditions such as diabetes and heart disease that make them vulnerable to severe COVID-19.

"Obviously, the data speak for themselves," says Fauci, whose institute helped support the study. He suspects that by late next month doses of one or both mRNA vaccines could start to be offered to people at highest risk from the coronavirus.

Many questions remain—about how long the protection offered by the vaccines will last, how safe they are, what regulators will demand to approve them, and how to meet the challenge of rapidly producing and distributing hundreds of millions, if not billions, of doses. Because warm temperatures cause the RNA and the lipid particles in which it is encapsulated to degrade, the vaccines must be kept frozen until days before use, requiring a cold chain to move them from manufacturing plants to pharmacies and clinics. In the short term, Moderna's vaccine may have an advantage for storage and transport as it proved to stay stable for long periods at –20°C, a normal pharmacy freezer tempera-

ture, whereas the Pfizer/BioNTech candidate appears to require ultracold freezers or dry ice to keep the product below −70°C.

Even −20°C is a challenge, and high-tech thermoses that were used to transport Ebola vaccines in sub-Saharan African countries at ultracold temperatures may be called into action. Longer term, Pfizer and BioNTech have said they intend to create a more stable freeze-dried powder formulation; another company, CureVac, said last week its COVID-19 mRNA vaccine remains stable at normal refrigeration and will soon start an efficacy trial.

Ruth Karron, who heads the Center for Immunization Research at the Johns Hopkins Bloomberg School of Public Health, notes another uncertainty: whether the mRNA vaccines prevent people from becoming infected in the first place, which is key to controlling the spread of the virus. "The data we have are that these vaccines protect you against severe illness, but it doesn't mean that you can't get infected and give it to your patient, your neighbor, your customer, or whomever." But Karron also says of the Moderna result: "Wow, fantastic, amazing."

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Operation Warp Speed, the U.S. government effort to develop COVID-19 vaccines and rapidly move them into efficacy trials, has invested $1 billion in Moderna's COVID-19 vaccine R&D. (Pfizer did not take Warp Speed money for development.) This summer, Warp Speed committed another $1.5 billion to Moderna to purchase 100 million doses of its candidate and $1.9 billion to Pfizer for the same amount of its product, which was developed at BioNTech, a company that has focused on treating cancer with mRNA.

Small studies have shown mRNA vaccines can trigger immune responses and don't have obvious, significant safety issues, but the two efficacy trials are the first to report that they can actually protect people from a pathogen. The snippet of mRNA at the heart of both vaccines was initially designed by a team led by Barney Graham of NIAID's Vaccine Research Center. When he learned that the strategy worked, Graham says, "I had my moment of relief and sobbing tears."

Both mRNA vaccines have yet to complete their trials, which aim to accrue about 150 to 165 cases of COVID-19 to provide greater statistical certainty about efficacy. They should hit those targets by December, when the U.S. Food and Drug Administration plans to convene an advisory panel to review the data. Cases are accumulating fast because most trial sites are in the United States, where the epidemic has exploded. If the advisers recommend emergency use authorizations for the vaccines, Warp Speed plans to start to deliver them to U.S. pharmacies and clinics the next day.

Moderna projects it can have about 20 million doses for the United States by the end of the year. Pfizer, which has made sales agreements with several countries in addition to the one it negotiated with Warp Speed, projects it can supply a total of 50 million doses by the end of this year, with an unspecified number going to Warp Speed. The U.S. Centers for Disease Control and Prevention will prioritize who should receive the vaccine first, but the companies say there should be enough to vaccinate the entire United States by the spring.

Both vaccines require two doses separated by weeks. Pfizer says it will have 1.3 billion doses next year. Moderna's vaccine delivers more mRNA—100 micrograms of mRNA per dose, versus Pfizer's 30 micrograms—and it does not see a way to produce more than about 1 billion doses in 2021. "We don't have a billion-dose manufacturing capacity sitting idle somewhere. We are increasing our output more and more and all our key engineers are working to make that happen," says Stéphane Bancel, Moderna's CEO.

The cost of the vaccine—Warp Speed paid about $25 per dose, all told—may also be far too high for many countries. Bancel says his company is in discussions with the COVID-19 Vaccines Global Access Facility, a nonprofit set up to help resource-limited countries purchase the vaccine at discounted prices.

Once supplies are available, the question will become whether people who are hesitant about a COVID-19 vaccine—especially a novel type that has no long-term safety record—will roll up their sleeves. Still, Karron suspects hesitancy will drop if people see the vaccine works and no serious side effects surface. She also imagines pressure will build to contribute to the social good. "There's going to come a moment where you're going to be able to say, you know, we could open up our community, except for people like you," Karron says. "If you would get vaccinated, we could get back to some semblance of life as we knew it."

Fauci says a COVID-19 vaccine always looked like a solid bet. The fact that many infected people clear the virus without developing serious, if any, symptoms, shows that the immune system can beat it back. "I've been saying all along that when the body tells you that it's capable of making an adequate immune response against natural infection, that tells you you have a pretty good chance to get a vaccine." ■

With reporting by Jocelyn Kaiser.

COVID-19

Reinfections, still rare, provide clues on immunity

The growing group of people who get sick twice suggests protection can wane relatively quickly

By **Jop de Vrieze**

In late June, Sanne de Jong developed nausea, shortness of breath, sore muscles, and a runny nose. At first, she thought it might be lingering effects from her COVID-19 infection in the spring. De Jong, 22, had tested positive on 17 April and suffered mild symptoms for about 2 weeks. She tested negative on 2 May—just in time to say farewell to her dying grandmother—and returned to work as a nursing intern in a hospital in Rotterdam, the Netherlands.

But when her symptoms re-emerged, her doctor suggested she get tested again. "A reinfection this soon would be peculiar, but not impossible," she told De Jong, who by then had again lost her sense of smell and had abdominal pains and diarrhea.

The call from her municipal health service came on 3 July. De Jong had tested positive again. "You're kidding me!" she recalls saying.

Scientists are keenly interested in cases like hers, which are still rare but on the rise. Reinfections hint that immunity against COVID-19 may be fragile and wane relatively quickly, with implications not just for the risks facing recovered patients, but also for how long future vaccines might protect people. "The question everybody wants to answer is: Is that second one going to be less severe most of the time or not?" says Derek Cummings, who studies infectious disease dynamics at the University of Florida. "And what do reinfections teach us about SARS-CoV-2 immunity in general?"

South Korean scientists reported the first suspected reinfections in May, but it took until 24 August before a case was officially confirmed: a 33-year-old man who was treated at a Hong Kong hospital for a

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